3.0 Non-Technical Abstract

This is phase I/II trial designed to test the safety and activity of genetically modified immune T cells in the treatment of lymphomas caused by the Epstein Barr virus emerging in immunodeficient bone marrow or organ transplant recipients or children with genetic immune deficiency diseases. The Epstein-Barr virus, in normal individuals, causes infectious mononucleosis. However, in immunosuppressed transplant recipients and certain patients with genetic immunodeficiencies, this virus can cause a lymphoma, that is a malignant disorder of white blood cells, called B-lymphocytes, which divide in an uncontrolled manner and can invade many organs producing wide-spread tumors that may involve lymph nodes, but may also involve the liver, the intestines, the lung or the brain. EBV lymphomas respond poorly to conventional cancer drugs and rarely, if ever, respond to anti-viral agents. Approximately half of these lymphomas may go into remission when treated with a monoclonal antibody directed against B cells. However, if the patients remain immunodeficient, a high proportion will suffer a relapse of disease.

Our center was the first to show that transfusion of white cells from immune donors could induce complete and lasting remissions of these lymphomas developing in bone marrow transplant recipients. Since then, studies have shown that the type of white cell responsible for controlling EBV lymphomas is an immune lymphocyte, called a T cell, which can kill EBV infected cells. However, a transfusion of lymphocytes from a transplant donor may also contain T lymphocytes that can react against the transplant recipient. If the donor and recipient are not genetically matched, this reaction, called graft-versus-host disease, can be severe and potentially lethal. An alternate approach to treatment involves transfusion of T cells that have been immunized to EBV in the test tube, over long periods of time. As these T cells grow in the test tube, EBV-reactive T cells are selected and cells that can potentially cause graft vs. host disease are deleted. However, it may take 5-7 weeks of culture before the T cells capable of reacting against the patient die out.

In this study, we propose an alternate approach. Lymphocytes from an HLA matched or partially matched donor will be re-immunized in the test tube with the donor's own EBV infected lymphocytes that have been irradiated to prevent their growth. After 8 days, the T cells will be infected with an onco-retroviral vector, called NIT, which encodes a mutant form of human nerve growth factor receptor which is biologically inactive and the herpes simplex virus thymidine kinase. Because T cells that have been previously immunized to an agent such as the EBV virus begin to proliferate as soon as they are exposed to this agent and because retrovirus selectively infect dividing cells, T cells that are immune to EBV are preferentially transduced. Because the vector transduced T lymphocytes express the mutant form of nerve growth factor receptor, they can be isolated with antibodies specific for the nerve growth factor receptor to high purity. These purified, genetically modified T lymphocytes will then be administered in graduated doses to groups of patients who have developed pathologically documented EBV lymphomas as complications of their transplants or their own genetic immune deficiency. The patients will then be closely followed for any evidence of toxicity and for the response of their EBV lymphomas to the T cells infusions. Because the T cells that have been genetically modified may also contain small numbers of T lymphocytes capable of reacting against the patient, the patients will also be closely monitored for evidence of graft vs. host disease. If graft vs. host disease develops, the patients will be

treated with ganciclovir, an antiviral agent which does not affect the growth of normal lymphocytes but will destroy T lymphocytes expressing the vector encoded herpes simplex virus thymidine kinase.

It is anticipated that the results of this phase I/II trial will provide important preliminary information regarding any toxicities that might be associated with the infusion of T lymphocytes genetically modified by the bicistronic onco-retroviral vector NIT. The doses of T lymphocytes administered would also be expected to induce regressions of EBV lymphoma. Thus, the trial will also provide initial information regarding the relative activity of these genetically modified T lymphocytes in the treatment of EBV lymphomas. Thirdly, because the T cells are transduced early after sensitization, they may contain small numbers of T cells that would be able to cause graft vs. host disease. In such a case, the trial will also provide an initial estimate of the susceptibility of T cells transduced with the NIT vector to treatment with ganciclovir. In addition, studies of those patients who do not receive ganciclovir should provide initial estimates of the contribution of the transfused genetically modified T cells to the redevelopment of the EBV specific T cell immunity and to any tumor regressions observed.